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September 29, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 10-61
Rockville, Maryland 20857

Re: Citizen Petition to Require 1) That the Active Ingredient of Generic Cefuroxime Axetil Products Be the Same as the Active Ingredient of Ceftin® Cefuroxime Axetil Products, and 2) That if FDA Nevertheless Were to Evaluate a Generic Product Containing Cefuroxime Axetil in Crystalline Form, That the Agency Impose Tight Controls for Solid State Form

Dear Sir or Madam:

CITIZEN PETITION

We are submitting this Petition on behalf of Glaxo Wellcome Inc. ("GW"), which markets cefuroxime axetil as Ceftin® Tablets and Ceftin® for Oral Suspension, under 21 C.F.R. § 10.30 and Federal Food, Drug, and Cosmetic Act ("FFDCA" or "Act") Sections 505(b) and 505(j), 21 U.S.C. §§ 355(b) and 355(j), to request that the Food and Drug Administration ("FDA") take the following actions:

A. Action requested

1. Petitioner requests that FDA not approve any abbreviated new drug application ("ANDA") or application filed under Section 505(b)(2) of the Act for any cefuroxime axetil product that includes crystalline cefuroxime axetil as all or part of the active ingredient.

2. If FDA nonetheless were to evaluate a generic product including any portion of crystalline cefuroxime axetil, Petitioner requests that FDA assure product quality, efficacy, and clinical performance by requiring tight drug substance and drug

product specifications for solid state form (including the content of individual polymorphs).

B. Statement of grounds

1. Background on Cefuroxime Axetil

Cefuroxime axetil is a broad-spectrum cephalosporin antibiotic. The drug substance used by GW is amorphous and contains a fixed ratio of diastereoisomers called isomers A and B. Ceftin® Tablets were approved by FDA in 1987 and are currently indicated for treatment of the following conditions: pharyngitis/tonsilitis, acute bacterial otitis media, acute bacterial maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis, uncomplicated skin and skin-structure infections, uncomplicated urinary tract infections, uncomplicated gonorrhea, and early Lyme disease (erythema migrans). Ceftin® for Oral Suspension was approved in 1994, and is indicated for acute bacterial otitis media, impetigo, and pharyngitis/tonsillitis.

The question of physical form (amorphous versus crystalline) of the active ingredient was pivotal to demonstrating substantial evidence of the efficacy of Ceftin® products and is pivotal to the approvability of any generic cefuroxime axetil product. Consistent with the current United States Pharmacopeia ("U.S.P.") monograph covering the drug substance, a copy of which is attached as Exhibit A to this petition, Ceftin® Tablets and Ceftin® for Oral Suspension are formulated from cefuroxime axetil in amorphous form, which GW found critical to achieving optimized bioavailability and dissolution (*see* discussion in section 3.b. below). Until July 2003, however, sponsors of ANDAs for cefuroxime axetil products will not be able to market a product formulated with a drug substance entirely or predominantly in amorphous form, without risking patent infringement. (The basic compound patent covering cefuroxime axetil in all forms expired in the United States on May 12, 2000.)

Therefore, at least until July 2003, sponsors of ANDAs for cefuroxime axetil products may be inclined to seek approval of products formulated with cefuroxime axetil drug substance wholly or partially in crystalline form. There is reason to believe that generic applicants are currently seeking approval to market formulations including crystalline cefuroxime axetil. There are two Drug Master Files for crystalline cefuroxime axetil currently listed on CDER's web site: DMF No. 14058 is described as "CEFUROXIME AXETIL (CRYSTALLINE) AS MANUFACTURED IN PUNJAB, INDIA" and is held by Ranbaxy Laboratories Inc., and DMF No. 14769 is described as "CEFUROXIME AXETIL CRYSTALLINE AS MFG IN INDIA THAILAND AND PUERTO RICO" and is held by Lupin Laboratories Ltd.

In addition to the Drug Master Files that have been submitted, the U.S.P. recently published for comment proposed amendments to the monograph for cefuroxime axetil that would accommodate products that contain crystalline cefuroxime axetil. In-Process Revision, *Pharmacopeial Forum*, Sept. – Oct. 2000, at 1277. The proposed amendments would delete the current restriction to amorphous form. The amendments were apparently sought by generic companies seeking approval of products including some proportion of crystalline cefuroxime axetil. In due course, GW will submit comments opposing the proposed changes, on the grounds, *inter alia*, that the quality, efficacy, and clinical performance of any formulation including crystalline cefuroxime axetil cannot be assured without tight controls for solid state form, including the content of individual polymorphs (*see* discussion in Section 3 below).

2. Approval of A Generic Product Containing Cefuroxime Axetil In Crystalline Form Would Violate Governing Law

As noted, the current U.S.P. monograph for cefuroxime axetil requires that the drug be in the amorphous form. GW submits that approval of an ANDA for a product formulated wholly or partially with the crystalline form of cefuroxime axetil would violate governing law for at least two reasons: 1) failure to satisfy the requirement that an ANDA drug contain the same active ingredient as the reference listed drug; and 2) failure to satisfy the requirement that the ANDA drug have the same labeling as the innovator product.

a. Failure to meet the "same active ingredient" requirement

Cefuroxime axetil wholly or partially in crystalline form is not the "same" active ingredient as amorphous cefuroxime axetil within the meaning of FFDCA Section 505(j)(2)(A)(ii)(I). *See also* 21 C.F.R. § 314.92(a)(1) (requiring that the active ingredient be "identical" to that in the listed drug).

Whether a generic product contains the "same" active ingredient as the listed pioneer product upon which it relies depends on whether the generic meets the standard of identity applicable to the listed drug. FDA has made it clear that compliance with the U.S.P. monograph for the listed drug is a minimum requirement, beyond which FDA may impose additional standards:

> FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that

> are material to the ingredient's sameness. For example, for some products, standards for crystalline structure or stereoisomeric mixture may be required.

57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992) (emphasis added).

The current U.S.P. monograph for cefuroxime axetil drug substance defines it as "a mixture of the amorphous diastereoisomers of cefuroxime axetil," and states under "Crystallinity" that "[i]t is amorphous." U.S.P. 24 at 356 (emphasis added). Under FDA's stated policy, the failure of cefuroxime axetil in crystalline form to meet the current U.S.P. standard of identity precludes its use in a generic drug whose ANDA refers to Ceftin® Tablets or Ceftin® for Oral Suspension.[1]

When FDA approved Ceftin® Tablets, it evaluated only the amorphous form of cefuroxime axetil. Indeed, the then effective antibiotic monograph described the drug as "amorphous and not crystalline." 21 C.F.R. § 442.19(a)(iii) (repealed) (emphasis added). (A copy of the former monograph is attached as Exhibit B to this Petition.) *See also* former 21 C.F.R. § 442.19(a) ("an amorphous mixture of the diastereo-isomers"). Although FDA repealed all antibiotic monographs in response to provisions in the Food and Drug Administration Modernization Act that removed separate approval procedures for antibiotics, 63 Fed. Reg. 26,066 and 26,127 (May 12, 1998), the former FDA antibiotic monographs are conclusive evidence of exactly what FDA approved when it approved Ceftin®. Because the antibiotic monograph for cefuroxime axetil was promulgated by FDA at the time of approval of Ceftin®, it reinforces and reflects the Agency's contemporaneous finding of the importance of the amorphous form to the proven quality of the drug.[2] The preamble to FDA's ANDA regulations, quoted above, makes it clear that among the standards that FDA may add to a U.S.P. monograph are "standards for crystalline structure." 57 Fed. Reg. at 17,959. Thus, even if the U.S.P. monograph did not specify that cefuroxime axetil be in amorphous form, FDA's policy,

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[1] As noted, the U.S.P. has published proposed modifications to the monograph for cefuroxime axetil that would address the use of crystalline material. Those changes have not been adopted by the U.S.P., and the U.S.P. has set a comment period lasting until February 15, 2001. As stated earlier, GW opposes the changes and intends to file comments with the U.S.P. GW submits that it would be improper for a generic applicant to rely on proposed changes, which may not be adopted, to justify a deviation from the active ingredient of a reference listed drug.

[2] Shortly after publication of the monograph in 1987, Eli Lilly and Company – professing an ability to achieve bioequivalence to Ceftin® Tablets with tablets of cefuroxime axetil entirely or partially in crystalline form – raised objections to the amorphous specification, as well as to other aspects of the monograph, and requested a hearing. Lilly subsequently withdrew its request for a hearing, and the monograph remained as originally published, with the critical specification of amorphous unchanged. *See* Docket No. 87-N-0317.

and previous findings as reflected in the antibiotic monograph, would still require the same result.

Pending ICH guidelines for specification of the solid state form of new drug substances and products are also instructive on the critical question of "sameness." *See* Draft ICH Guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances." 62 Fed. Reg. 62,890 (Nov. 25, 1997). The draft ICH guidance identifies as appropriate methods for characterizing solid state forms the following: x-ray powder diffraction ("XRPD"), spectroscopy, microscopy, and thermal analysis. *See* Decision Trees #4, Question 1, 62 Fed. Reg. at 62,901. Amorphous and crystalline forms tend to differ in every one of these tests (*see* discussion below of data on the different forms).

In addition, the FDA Draft Guidance for Industry entitled "BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation" (Nov. 1998) states, in an analogous context: "Generally, only two physical properties of the drug substance, morphic form and particle size, are considered critical for evaluation of equivalence. . . . The physical properties of the drug substance will be considered equivalent after a given change if at least three postmodification batches of the drug substance are prepared and the data demonstrate: Conformance to established acceptance criteria for morphic form or, where acceptance criteria do not exist, the isolation of the same form or mixture of forms within the range of historical data . . . ." *Id.* at p. 7, lines 192-99.

In summary, the U.S.P. monograph's description of this drug as an amorphous compound, as well as concepts of "sameness" embodied in the statute, FDA regulations, and FDA and ICH guidances, preclude the approval of a generic cefuroxime axetil product including any proportion of crystalline drug substance. However, even if the U.S.P. monograph were not so specific, or were changed to permit crystalline drug, FDA should, in light of its previously stated policy and the significant product quality ramifications (*see* below), require the amorphous form. This would assure consistency with the product that was tested and approved, as illustrated by the former FDA antibiotic monograph. Indeed, as FDA has made clear in the context of a protein product with natural variability, no variation of active ingredient in a generic product should be permitted unless, in addition to exhibiting "clinical equivalence to the pioneer," the generic shows "chemical identity to the extent possible . . . ." *See Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1321 (D.C. Cir. 1998). Here, since there is absolutely no

question about the technological feasibility of matching the amorphous form of cefuroxime axetil in Ceftin® products,[3] identity should be required.

b. Failure to meet the "same labeling" requirement

The package insert for Glaxo Wellcome's cefuroxime axetil products describes the active ingredient as being "in the amorphous form." (A copy of the current labeling is attached as Exhibit C to this Petition.) Approval of a drug wholly or partially formulated with the crystalline form of cefuroxime axetil would, therefore, also flout the requirement that the labeling of an ANDA product be the same as that of the reference listed drug. FFDCA Section 505(j)(2)(A)(v). The only differences in labeling permitted by FDA regulations are with respect to "expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity." 21 C.F.R. § 314.94(a)(8)(iv). The issue of "amorphous" versus "crystalline" is a difference in active ingredient, not of formulation.[4] Thus, a generic version of cefuroxime axetil cannot be approved unless its labeling states that the active ingredient is in the amorphous form. If, in fact, the active ingredient is wholly or partially in crystalline form, such a labeling statement would be false, and therefore untenable. Thus, on that ground as well, a generic product whose active ingredient is not in amorphous form is not eligible for approval.[5]

Similarly, because a generic product whose active ingredient is wholly or partially in crystalline form would not meet the current U.S.P. monograph, it would have to bear labeling that differed from the listed drug with respect to the name of the drug, and would also be unapprovable on that basis. Such a product would be misbranded if it did not bear a name that was "clearly distinguishing and differentiating from any name recognized" in the U.S.P. (*i.e.*, cefuroxime axetil), because it would not comply with the standard of identity currently prescribed in that compendium. 21 C.F.R. § 299.5(a).

This same labeling requirement is unequivocal in the statute. Thus, even if FDA were to conclude that it supported the pending proposed change in the U.S.P.

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[3] A DMF for cefuroxime axetil in amorphous form (No. 14653-Fako Ilaclaria AS) is apparently already on file.

[4] As such, this situation is distinguishable from the labeling differences permitted for generic propofol products because of a difference in formulation. *See Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000).

[5] GW notes that the proposed amendment to the U.S.P. monograph for cefuroxime axetil would require that the labeling state whether the cefuroxime axetil was crystalline or amorphous. Thus, if the proposed amendment were adopted, no crystalline product could be approved under an ANDA, because the labeling of that ANDA product would necessarily have to be different from that of the innovator in a manner not permitted by the statute or FDA regulations.

monograph – and GW explains below why FDA should not – the statute unambiguously prohibits approval of a generic product that does not conform to the innovator drug's labeling in this respect.

3. FDA Must, to Assure Product Quality, Efficacy, and Clinical Performance, Require That Any Formulation Including Crystalline Cefuroxime Axetil Be Tightly Controlled For Solid State Form (Including the Content of Individual Polymorphs)

As noted, GW's Ceftin® products contain a strictly amorphous combination of two diastereosomers (A and B) in a fixed ratio. Introducing crystalline material into the formulation raises the specter of one batch of the drug differing significantly from the next (and of marketed batches differing significantly from the batch tested in bioequivalence testing) because of the multitude of forms in which crystalline cefuroxime axetil exists, and their differing properties. Consequently, if a formulation of cefuroxime axetil includes crystalline material, it must be tightly controlled for solid state form (including the content of individual polymorphs) through establishment of appropriate drug substance and drug product specifications.

As discussed further below, cefuroxime axetil can exist in at least the following seven solid state forms: amorphous isomer A, amorphous isomer B, three forms of crystalline isomer A – to which we refer as AI, AII, and AIII (a dioxane solvate) -- and two forms of crystalline isomer B – BI (anhydrous) and BII (hemihydrate). Each of these different forms has a different solubility.[6] Thus any given batch could contain any one of a myriad of combinations of these seven forms, with the variability giving rise to potential variability in product quality, efficacy, and clinical performance. As one example, a batch that is ¼ amorphous A, ¼ crystalline AI, ¼ amorphous B, and ¼ crystalline BI would predictably have greater solubility than a batch containing ½ crystalline AII, ¼ crystalline BI and ¼ crystalline BII. Conceivably the former batch might pass a bioequivalence test against Ceftin® Tablets or Ceftin® for Oral Suspension, while the latter might fail to produce adequate blood levels to treat a patient's infection.

Regulatory authorities expert in pharmaceutical science (including FDA) have developed an analytical framework to deal with the type of problems that would be presented by a product such as a generic cefuroxime axetil that deviates from the approved all-amorphous form. *See* Decision Trees #4, Question 3 in Draft ICH Guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances

[6] The solubility of the AIII form has not been determined because it is not a pharmaceutically acceptable substance and is thus not relevant to the analysis.

and New Drug Products: Chemical Substances." 62 Fed. Reg. 62,890, 62,902 (Nov. 25, 1997).[7]

a. The ICH Guidance

The regulatory construct suggested by the ICH draft guidance is logical and, we submit, must be followed here to assure product quality, efficacy, and clinical performance: First, one determines if there are different solid state forms. Here, there are 6 relevant forms. Second, one determines whether those forms have different properties. Here, they differ dramatically in solubility. Finally, in light of evident differences with the potential to have an adverse impact on product performance, one establishes acceptance criteria adequate to achieve the necessary control and consistency. Given the complexities of the solubility profile exhibited by cefuroxime axetil, and the implications for bioavailability, such criteria must apply to the drug product as well as the drug substance: product performance testing, such as conventional dissolution tests, are not adequate safeguards against compromised clinical performance.

Moreover, because there is the potential – even the likelihood – of interconversion of different forms, the regulatory controls must apply 1) after manufacture of the active drug substance, 2) after manufacture of the drug product, and 3) on stability.

GW recently engaged Dr. Stephen Byrn, Charles B. Jordan Professor, and Head of the Department of Industrial and Physical Pharmacy, at Purdue University, and Chairperson of FDA's Pharmaceutical Science Advisory Committee, to contribute to an assessment of product quality and performance ramifications of introducing crystalline material into cefuroxime axetil products. He directed a study conducted under the auspices of SSCI, Inc. A declaration stating Dr. Byrn's views and describing his findings is attached as Exhibit E to this Petition (hereinafter referred to as the "Byrn Declaration"). As\set forth below, his data support the GW position that products containing crystalline material in any amount would likely have different quality characteristics, including different solubility, than Ceftin® products.

Dr. Byrn followed Decision Trees #4 of the draft ICH Q6A document. He performed a polymorph screen and determined that crystalline diastereoisomer A can exist as three crystalline forms (designated AI, AII and AIII (a dioxane solvate)) and that crystalline diastereoisomer B can exist in an anhydrous form (designated BI) and a hemihydrate form (designated BII). Byrn Declaration at ¶ 6. Following the Decision

[7] *See* Exhibit D. Although the Decision Trees use the word "polymorph," it appears from the text of the draft that the same decision process would apply to other variations of "solid state" form, such as the difference between amorphous and crystalline forms. *See, e.g., id.* at 62,894.

Trees #4, he characterized the various polymorphs that he had identified using state-of-the-art methods referred to in the Draft ICH Guidance – the various forms exhibited distinctive characteristics. He then proceeded to evaluate whether the various forms of cefuroxime axetil have different properties with a potential impact on safety, performance, or efficacy. This included, most critically, a comparative assessment of the solubility of the various solid state forms. Aqueous solubility was measured using the dissolution of each form over time. The solubility of diastereoisomer A ranged from 0.6 mg/mL for amorphous substance to 0.02 mg/mL for crystalline diasteroisomer AII. Similarly, the solubility of diastereoisomer B ranged from 1.3 mg/mL for amorphous substance to 0.2 mg/ml for crystalline diasteroeisomer BII. These data show that the solubility of the various components of an amorphous-crystalline mixture could vary 65-fold. Byrn Declaration at ¶ 8.

The differential solubilities of the crystalline isomers could cause *in vivo* dissolution and absorption to vary markedly from one generic batch to the next, even if the overall ratio of amorphous to crystalline material remained constant, if there were underlying variation in the relative proportions of the crystalline isomers. The need for robust analytical controls, for both release and stability testing purposes, is evident. Dr. Byrn states in his declaration that, "differences as dramatic as those exhibited by the various forms of cefuroxime axetil can certainly be expected to affect product quality and performance, because as a general matter, solubility tends to correlate with *in vivo* dissolution, absorption, and bioavailability." Byrn Declaration at ¶ 9. In addition, Dr. Byrn notes the possibility that the presence of crystalline cefuroxime axetil drug particles could reduce the bioavailability of whatever amount of amorphous material is included in an admixture, further compounding the potential adverse impact of including comparatively less-soluble crystalline material in a formulation. Byrn Declaration at ¶ 10.

The bioavailability differences between crystalline and amorphous forms anticipated by Dr. Byrn are confirmed by *in vivo* data.[8] Dr. Byrn reviewed bioavailbility data supporting GW's choice to formulate Ceftin® Tablets exclusively with the amorphous form (*see* discussion below of these data), and he notes that crystalline material "unmistakably exhibits inferior bioavailability in comparison to amorphous material." Byrn Declaration at ¶ 9.

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[8] That cefuroxime axetil is much more soluble in the amorphous form than in the crystalline form, *in vitro*, was shown by earlier GW testing. (*See* Table in Exhibit F to this Petition containing experimental data on file at Glaxo Wellcome concerning the comparative aqueous solubilities of the crystalline and amorphous forms of cefuroxime axetil.) The superior bioavailability of amorphous cefuroxime axetil is thought to be a function of its ability to induce supersaturation of an aqueous solution and therefore a level of solubility several times greater than that of the crystalline form.

GW originally decided to develop an amorphous product on the basis of a study[9] comparing the urinary recoveries[10] of cefuroxime in 12 healthy subjects dosed in the fasted state with both crystalline and amorphous forms of cefuroxime axetil as an aqueous suspension. In this study, micronized and unmicronized varieties of each form of the drug were administered in order to determine the effect of particle size on absorption. The 0-12 hour urinary recovery of cefuroxime was statistically significantly lower with both micronized and unmicronized drug given in the crystalline form as compared with the amorphous. The ratio of urinary recoveries for crystalline to amorphous (0.75) was less than 0.8, thus indicating bioinequivalence according to standard criteria.

Subsequent comparative studies have generally reinforced the initial conclusion that crystalline material is absorbed less well, although the difference was only detected in larger studies. In one pilot, six-subject cross-over design study[11] in which aqueous suspensions (250 mg) of amorphous and crystalline cefuroxime axetil were compared in the fed state, no differences were observed in the serum pharmacokinetic parameters of C_{max}, T_{max}, and AUC. However, two larger studies revealed differences. In these two studies, each of cross-over design, the marketed amorphous tablet formulation (250 mg) served as the reference drug, and simple aqueous suspensions of crystalline material (250 mg) were evaluated by blood level and urinary recovery measurements in 24 healthy volunteers. In one of these 24-subject comparative studies[12], dosing took place in the fed state only, and three different crystalline formulations (each of two crystalline diastereoisomers, and the racemic mixture) and the amorphous tablet were evaluated. All three of the crystalline formulations tested bioinequivalent to the amorphous tablet, given comparative results for serum pharmacokinetic parameters (C_{max} and AUC) and 24-hour urinary recovery that all fell outside the range 80-120%. (For the crystalline racemic mixture, the ratios to the amorphous product were as follows: C_{max} – 0.51; AUC – 0.62; and 24-hour urinary recovery – 0.59.) In the other of these 24-subject studies[13],

[9] Report No. HVT/80/30, "Human Volunteer Trial to Investigate the Urinary Recovery of Cefuroxime After Single Oral Doses of 250 mg Cefuroxime as E47 Ester in Three Different Forms" (1980). (A copy of this Report is attached as Exhibit G to this Petition.)

[10] Cefuroxime is excreted unchanged in the urine.

[11] Report No. GMH/87/021, "To Compare the Serum Level Profile of Amorphous and Crystalline Cefuroxime Axetil; A Pilot Study With Dosing After Food" (1987). (A copy of this Report is attached as Exhibit H to this Petition.)

[12] Report No. UCP/89/028, "An Evaluation of the Bioequivalence of Cefuroxime Axetil Crystalline Isomers and Tablets in Healthy Adult Male Volunteers" (1989). (A copy of this Report -- without appendices -- is attached as Exhibit I to this Petition.)

[13] Report No. GPK/91/003, "A Study to Assess the Relative Bioavailability of Cefuroxime from an Oral Aqueous Suspension of Crystalline Cefuroxime Axetil in Comparison with an Amorphous Tablet in the Fed and Fasted State" (1991). (A copy of this Protocol -- without appendices -- is attached as Exhibit J to this Petition.)

there was a pronounced difference as between crystalline and amorphous formulations (ratio 0.69) in C_{max} in the fed state, smaller but statistically significant differences in C_{max} in the fasted state, and comparable AUC in both states, with 12-hour urinary recovery data not indicative of inequivalence.

b. Necessary Controls

Even if the Agency were inclined to permit the use of crystalline cefuroxime axetil in generic cefuroxime axetil products (legal considerations notwithstanding), consistent and reliable product performance would require tight acceptance criteria to assure no batch–to–batch or stability–related variation in 1) the ratio of crystalline to amorphous drug, 2) the ratio of diastereoisomers, or 3) the ratios of polymorphs, in each batch. As Dr. Byrn has stated: "In the absence of tight specifications that respond to the widely disparate solubility properties of the various forms by demanding consistency in the precise mix of crystalline polymorphs, as well as the overall permitted proportion of crystalline material in an admixture with amorphous, there can be no assurance of consistent absorption, bioavailability, and clinical performance of the drug." Byrn Declaration at ¶ 11. As noted, GW's development work suggests that introducing crystalline cefuroxime axetil into the product may result in reduced bioavailability. Given this, GW submits that, at a minimum, the Agency must control any permitted use of non-amorphous material in conjunction with amorphous material by calling for tight specifications for the relative proportions of the different forms in both the drug substance AND the drug product. As to the drug product, standard performance testing alone, *e.g.*, conventional dissolution testing, is simply not adequate to contend with the complexities surrounding the variability in solid state form of cefuroxime axetil. Byrn Declaration at ¶ 11. Similarly, for the drug substance, Stephen Byrn *et al.*, "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations," Pharm. Res. 1995, at 945-54, a copy of which is attached for your review as Exhibit K, suggest that for mixtures of crystalline and amorphous forms, quantitative analytical controls should be required. Such specifications, GW submits, should be established with strict reference to the relative proportions of crystalline and amorphous material, as well as the underlying proportions of the various crystalline forms, in the "biobatch" (as well as component drug substance) of generic products that are compared to Ceftin® products in bioequivalence testing.

It would not be sufficient to impose such specifications on the active pharmaceutical ingredient alone, because that would overlook the possibility of significant variation in solid state form associated with secondary manufacturing steps taking place after testing and release of the drug substance. *See* Byrn Declaration at ¶ 11. Secondary manufacturing steps could vary the proportion of crystalline and amorphous material in a mixture, or the underlying proportions of the various crystalline forms. To

cite just one example, Ranbaxy Laboratories, an organization identified earlier in this Petition as the holder of a Drug Master File for crystalline cefuroxime axetil, has filed an international patent application ("Process for the Preparation of Cefuroxime Axetil in an Amorphous Form") that claims a manufacturing method whereby crystalline cefuroxime axetil drug substance is combined with one or more pharmaceutically acceptable excipients, and then milled until it is converted to amorphous material. The application specifies that the claimed milling process may take place with mortar and pestle, or with commercially available milling machines that work on substantially the same principle. (For reference, a copy of the patent application is attached as Exhibit L to this Petition.)

Steps such as combining an active pharmaceutical ingredient with one or more excipients, and milling, are common to secondary manufacture, and typically take place after release of the active pharmaceutical ingredient against established specifications. However, if such processing steps are designed and employed to manufacture cefuroxime axetil products with a necessary target proportion of amorphous material, toward the goal of acceptable biovailability, confirmation of crystalline-amorphous and polymorph ratios after manufacture would be absolutely critical. In the absence of tight specifications for the proportion of amorphous drug substance in cefuroxime axetil products manufactured according to such a process, and for the content of individual polymorphs, there would be no assurance of adequate control of bioavailability. In such circumstances, specifications pertaining only to the drug substance, as it is tested and released prior to secondary manufacturing, would not suffice.

Consistent with the essence of the Draft ICH Q6A Guidance document, where both crystalline and amorphous cefuroxime axetil are used to manufacture product, specifications for the relative proportions of each (including the content of individual polymorphs) must be included as part of governing quality standards for stability testing and at end of life, as well as at release. It is well known that the presence of crystalline nuclei can "seed" amorphous materials and reduce the time to recrystallization. *See* Byrn Declaration at ¶ 11. It has been demonstrated by Saleki-Gerhardt and Zografi, "Non-Isothermal and Isothermal Crystallization of Sucrose from the Amorphous State," Pharm. Res., 1994, at 1166-73, a copy of which is attached as Exhibit M to this petition, that the induction time to recrystallization can be reduced by the presence of crystalline material and can be especially marked when amorphicity has been induced by milling the parent crystals. Byrn *et al.* (Pharm. Research 12 (7) at 945-54, Exhibit K) suggest that for drug substances where a mixture of crystalline and amorphous forms is produced, quantitative analytical controls should be used to monitor the proportions of amorphous and crystalline content at the time of batch release and during stability studies. Furthermore, Decision Trees #4 in ICH Guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical

Substances" recommends that in cases where a drug substance may exist in different solid state forms and drug product performance testing does not provide adequate control if the polymorph ratio changes, polymorphic form should be monitored for change during stability testing of the drug product. 62 Fed. Reg. 62,890, 62,902 (Nov. 25, 1997). Therefore, maintenance of the established crystalline/amorphous proportions (including adequate control of the ratios of the various crystalline forms of the A and B isomers) should be considered an indispensable element of the stability assessment of drug substance and dosage forms including amorphous cefuroxime axetil as part of a crystalline/amorphous mixture. The potential consequence of not controlling and monitoring the proportions over time would be to compromise product quality and efficacy.

At a time of rising concern about the public health threat posed by the emergence of microbial resistance to antibiotics, the potential for compromised product quality and efficacy is all the more serious. *See* "Proposed Rule: Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use," 65 Fed. Reg. 56,511 (Sept. 19, 2000). The well-recognized danger of suboptimal plasma and tissue concentrations of an antibacterial drug in humans is that of more rapid selection of microorganisms with diminished susceptibility to the drug, as well as potentially to other antibiotics in the same pharmacologic class. The potentially poor clinical performance of an inadequately controlled generic substitute for a Ceftin® product could well exacerbate the danger of microbial resistance.

Dr. Byrn concluded by stating: "In my professional opinion, a product that introduces crystalline material into a formulation of cefuroxime axetil is not designed for optimal stability, bioavailability and clinical performance. The scientific and regulatory considerations . . . deserve serious attention and are important to the public health." Byrn Declaration at ¶ 12. To address such concerns, if FDA does decide that it can approve a generic version of cefuroxime axetil that includes some amount of crystalline drug, the generic manufacturer must be required to assure, through appropriate drug substance and drug product acceptance criteria, that each marketed batch matches the batch shown to be bioequivalent to Ceftin® in ratios of amorphous to crystalline drug, of stereoisomers, and of polymorphs. Such specifications must govern for both release and stability purposes.

The failure to impose such specifications would be a failure to assure that the marketed generic was bioequivalent to Ceftin®. Such an abdication of the Agency's obligations would, we respectfully suggest, constitute agency action that is "arbitrary and capricious" in violation of applicable law.

C. Environmental impact

This petition requests that FDA not approve applications for a drug product or that FDA place conditions on such approval. Because the requested action would not increase the use of the active moiety, the petition is subject to a categorical exclusion from the requirement of an environmental impact assessment. *See* 21 C.F.R. § 25.31(a).

D. Economic impact

Information on the economic impact of this petition will be submitted if requested by the Commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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